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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,712	SCHEULE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7,9-16 and 18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7,9-16,18 and 20-25* is/are rejected.

7)☐ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1, 2, 8, 13, 17 have been canceled, claims 3-7, 9-16, 18, and 19 have been amended, and claims 20-25 have been added by the amendment dated July 14, 2004.

Claims 3-7, 9-16, and 18-25, to which the following grounds of rejection remain and/or are applicable, are pending.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7, 9-16, 18, 20-25 readable on a genus of cationic molecules, when read in light of the as-filed specification (page 6), clearly embrace an enormous number of non cationic lipid based moelecules. These cationic molecules when complexed with a CpG containing oligo, according to the disclosure of the specification must be able to provide an anti-tumor effect. As such, these claims are claimed generically, and thus, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification only provides sufficient written description of CpG motif containing oligonucleotides complexed with a cationic lipid, which can be claimed generically as such. However, the claims are broadly drawn to other species of cationic molecules which are yet to be discover, or yet to discover sufficiently so as to reasonably render the generically claimed subject matter adequately described by applicant at the time the invention was made.

As such, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified sequence that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to "cationic molecule" with no chemical structure as claimed in the presently pending claims because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other material(s) of agents other than those known in the prior art, as admitted by the as-filed specification, having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of cationic molecules as essential components of the claimed anti-tumor treatment compositions, which must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents*

of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of a representative number of species of cationic molecules, which are clearly claimed generically, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 3-7, 9-16, 18, 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling:

1/ A method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid and an immunologically active nucleic acid sequence that does not encode for an expressible tumor-associated antigen, wherein the nucleic acid sequence contains at least one immunologically active CpG motif, and wherein said composition is administered in an amount effective to stimulate said anti-tumor cell immune response;

2/ A method of prolonging the survival of a tumor bearing mammal comprising the step of

administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active CpG motif containing nucleic acid sequence does not encode for an expressible tumor-associated antigen, wherein said complex is provided in an amount effective to stimulate a protective anti-tumor cell immune response, thereby prolonging the survival of the tumor bearing mammal, and wherein said cationic molecule is the compound GL-67.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

1/ Issue regarding the use of a generic cationic molecule, which is not necessarily a cationic lipid compound.

The claims as written are reasonably being interpreted as embracing non-lipid cationic molecules. The specification as a whole only teaches and provides sufficient guidance for the making and use of a complex comprising a cationic lipid compound and an immunologically active CpG motif containing nucleic acid sequence. However, the claims are not necessarily limited to such complexes wherein a cationic lipid compound is employed, nor the specification provides any guidance as to what is exactly the structure of cationic molecules other than cationic lipids. In fact, the specification teaches as a whole that the presence of both a CpG motif containing nucleic acid sequence and a cationic lipid compound is essential for the efficacy in generating an anti-tumor immune response. As such, the information regarding cationic molecules other than cationic lipids must present in the disclosure. While it is generally understood in the art of record that cationic amphiphiles, cationic lipids, and cationic polymers have been used enhance the delivery, stability and therapeutic efficacy of an expressible DNA molecule or a non-expressible CpG motif containing DNA, the state of the art of record is silent as to an interchangeable use of such a cationic molecule as a non-expressible DNA vaccine complex in a cancer prevention treatment in an individual. In fact, cationic lipids compounds are structurally distinct and are expected to behave unpredictably in an *in vivo* environment. The specification focuses mainly on cationic amphiphiles or cationic lipids, and all of its working examples involve the use one particular lipid compound, the GL-67. The specification does not provide any disclosure so as to enable a skilled artisan to make and use sufficient amount and types of cationic molecules other than cationic lipids so as to sufficiently cover the breadth of such broadly claimed "cationic molecules". Even with claimed

embodiments drawn to cationic lipid based complexes for use in DNA therapeutic applications, Filion (International J. of Pharmaceutics, 162:159-170, 1996), states:

[t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.

Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).

These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

As such, with respect to claim 7, 18, and claims dependent there from the claimed invention is only reasonably enabling for claims that claim specifically:

A method of prolonging the survival of a tumor bearing mammal comprising the step of

A method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active CpG containing nucleic acid sequence, wherein said complex is provided in an amount effective to stimulate a protective anti-tumor cell immune response, thereby prolonging the survival of the tumor bearing mammal, and wherein said cationic molecule is the compound GL-67.

3/ Issue regarding claims drawn to a method of generating a protective anti-tumor response in a mammal including primates such as subjects having a tumor, wherein the method generates immune memory against the established tumor, thereby eliminating the tumor. See claims 23 and 25. The specification contemplates, for example, on page 4 bridging page 5 that a protective anti-tumor response is a protective anti-tumor response that may provide long term protective immune memory. The specification does not provide any closed definition as to what is meant by the "long term protective immune response" nor does the specification identify and/or provide any information regarding an "immune memory" generated by the claimed methods. As such, and in view of the customary and ordinary meaning of the "long term protective immune memory" in the art, the claimed invention as claimed in claim 7 and claims dependent there from would embrace a method of curing a mammal such as primates including tumor bearing humans, domestic mammals, and farmed mammals from having a tumor or cancer, since the claims explicitly state that the tumor is eliminated. Nowithstanding the lack of a prior art that teaches any drug that could be used to eliminate a cancer, and notwithstanding the complex nature of cationic lipids, which is structure independent, and its effect for use as a tumor vaccine in tumor bearing patients, the claims also embrace a large number of tumors such as melanoma, breast tumor, ovarian tumor, pancreatic tumor, colon tumor, brain tumor, liver tumor, leukeumia, and stomach tumor. The

state of the prior art exemplified by Filion, McCluskie *et al.* not only does not teach or even suggest that it is routine or conventional in the art to employ any form of DNA complex as a cancer vaccine so as to provide a protective anti-cancer effect so as to eliminate a tumor, but also suggests that while it may be conventional in the prior art to employ a CpG motif contaiing DNA to treat therapeutically a tumor bearing mammal, notably in the form of increasing a Th1 immune resposne or cytokine induced inflammatory response in small animals such as mice or rats, the state of the art of DNA cancer vaccine, whereby a completely protective response is generated, remains reasonably unpredictable at the time the invention was made. More specifically,

McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teaches that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the

antigen" (page 297, column 1).

Lee *et al.,* Critial Reviews in Therapeutic Drug Carrier System, 14, 2:173-206, 1997, states:

> Because gene transfer efficiency is determined by a large number of factors, many of which are not well understood, it is difficult to predict the performance of a specific cationic liposome formulation based simply on the cationic lipid structure and/or the lipid composition. The gene transfer property of a vector is determined by 1) particle (DNA/lipid) size; 2) lipid composition; 3) lipid/DNA ratio; 4) formulation procedure; 5) DNA concentration; 6/ strength and tissue specificity of the promoter and enhancer elements; 7) for *in vitro* gene delivery, cell line, duration of transfection, cell confluency level, presence or absence of serum, etc; For *in vivo* delivery, route of administration (page 184);

While the strength and tissue specificity of the promoter and enhancer elements are not required for the claimed invention wherein a non-expressible DNA is employed as an immunologically active DNA as one of the main components in a cationic lipid/DNA complex, the state of the prior art does suggest and teach that the *in vivo* behaviors and/or activities of one particular or other cationic lipid/DNA complexes cannot be reasonably extrapolated from that of another particular cationic lipid/DNA complex.

The specification as a whole provide a number of working examples, which focus mainly on the efficacy of the GL-67/CpG motif containing DNA sequence (expressible or non-expressible) in generating a therapeutically relevant immune response in a number of different tumor established (xenografted) mice and rats. In the mice and rat models, not only the generated immune response appears to be sufficient to inhibit the growth of the xenografted tumors, it is also sufficient to prolong the survival of the treated mice and rats. Coupled with state of the prior art regarding the well-established immunotherapeutic activities of CpG motif containing nucleic acid sequences in inhibiting the growth of a tumor in a tumor model such as mice or rats, the application is reasonably enabling for claimed embodiments, drawn specifically to a method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active nucleic acid sequence that does not encode for an expressible tumor-associated antigen, wherein said composition is administered in an amount effective to stimulate said anti-tumor cell immune response;

However, neither the specification nor its working examples provide substantial evidence demonstrating an anti-cancer protective effect in any tumor bearing individual or art-recognized animal model, on which a person skilled in the art could reasonably conclude that a cationic lipid/DNA complex(es), regardless of whether the DNA is expressible or not, is or are effective for use as a master vaccine in eliminating any type of cancers or tumors in an vaccinated individual. One closest example, example 8, provides an ovarian tumor (MOT) bearing mouse model, in which a generated immune response is sufficient to prolong the

survival of the mice against the fist challenge and subsequent challenge of MOT tumor cells, *e.g.*, 2, 9 and 16 days. On the basis of this prolonged survival wherein no particular time period is provided, Applicants then suggest that the result indicates a formulation-dependent generation of a protective, memory-based immune response that was systemic in nature, and that this is sufficient to provide patentability for the broad claimed invention as set forth in claim 7. However, a close review of the working example does indicate the followings: 1/ the prolonged survival period was only measured at most for 16 days, 2/ not only the GL-67/DNA is used as a priming antigen, the subsequent challenge of the same MOT tumor cells wherein the immune response was already primed specifically against the established MOT tumor cells is not indicative of a protective effect against any formation of an endogenous tumor wherein no specifically primed immune response is present or activated; and 3/ the experiments was employed in an already MOT tumor grafted in mice. Thus, these deficiencies and/or non-correlative factors are not deemed sufficient to lead on skilled in the art to reasonably conclude that the GL-67/DNA complex is effective for use as a DNA vaccine for preventing a formulation of an endogenous ovarian tumor in a tumor-free individual, let alone other claimed embodiments wherein an enormous number of other cationic lipid/DNA complexes are claimed as cancer vaccine(s). At best, the working example 8 coupled with the guidance provided by the as-filed specification provides substantial evidence showing that one skilled in the art not only could use GL-67/CpG containing DNA complex in therapeutically combating the growth of a tumor in a mammal, the complex surprisingly could be used to prolong the survival of a tumor bearing mammal.

To further substantiate unpredictable factors involved in using a particularly type of cationic lipid complex, which has not been shown to provide any anti-cancer protective effect, Filion (International J. of Pharmaceutics, 162:159-170, 1996), states:

> [t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.
>
> Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).
>
> These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

Notwithstanding the complexities associated with the use of a cationic lipid as a main component in an anti-cancer vaccine, McKenzie, Immunologic Res, 24,3:225-244, 2001, states (page 232, column 1) that "CpG DNA, when added as an adjuvant with a DNA vaccine, gave

no further enhancement of CTLs in one study". McKenzie also states on page 232:

> There is also another level of complexity for CpG motifs. The optimal motif for stimulation differs between species. CpG motifs can also be immuno-suppressive or neutralizing, depending on the context of flanking residues.

Agrawal, TRENDS in Molecular Medicine, Vol. 8, 3:114-121, 2002, states:

> The DNA sequences containing an unmethylated CpG dinucleotide flanked by two purine bases on the 5'-side and two pyrimidine bases on the 3'-side, such as GACGTT, were found to activate the mouse immune system efficiently. However, the human immune cells responded poorly to this hexameric motif, suggesting that the sequences required for CpG-related immune stimulation varies from species to species (page 114 through page 115).

> The pattern and kinetics of induction of the cytokines *in vivo* depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (page 115, last full paragraph).

These unpredictable factors as expressed in the art of record clearly provide substantial evidence showing that the claimed invention as claimed specifically in claim 7 and claims dependent there from is not reasonably enabling to its full breath at the time the invention was made, particularly on the basis of the as-filed application.

Thus, in view of the lack of any established nexus between the guidance provided by the as-filed specification including the *in vivo* data shown in the working examples and the subject matter being sought in the claims, one must evaluate the evidence presented and determine whether applicant has demonstrated such correlation or a reasonable likelihood of such. In the instant case, the data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility of the claimed invention as broadly claimed. This conclusion coupled with state of the art, as indicated in the stated Office actions, is consistent with a finding of lack of enablement for the practice of what is claimed. The as-filed application fail to address these art-recognized limitations with regard to the unpredictability of claiming a full breadth encompassing a generic cationic lipid/DNA complex for use to generate anti-cancer protective responses in an individual at the time the invention was made. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, it is not apparent as to how a skilled artisan, without any undue experimentation, reasonably extrapolates from the applicant's disclosure including the shown animal model to the entire breadth of the claims. It is not apparent then how one skilled in the art, without undue experimentation, practices the claimed invention, and/or uses a broadly claimed cationic molecule/DNA complex as a DNA cancer vaccine to provide an active and protective immunity so as to eliminate a tumor in a mouse or small animal, let alone a the full scope of a "mammal", particularly on the basis of applicant's disclosure, and in view of the doubts expressed in the art of record at the time the invention was made.

Note that even while one of applicant's cationic lipid/DNA complex exhibits an efficacy in prolonging the survival of the treated rats or mice, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

Applicant's response (pages 5-7) has been considered fully by the examiner, but is not found persuasive because of the remaining issues as set forth in the above stated rejection, and because of a broadly claimed subject matter as currently present in the amended claims.

More specifically, Applicant asserts that given the fact that polyamines and polyethyleninimes have been routinely employed in the prior art as a delivery vector for nucleic acid molecules, the breadth of "cationic molecules" is reasonably enabled at the time the invention was made (page 6). However, the issue is not that the examiner disputes the fact that polyamines and polyethyleninimes were available in the prior art as nucleic acid delivery vectors. Rather, the issue is that the as-filed specification only teaches one single species of cationic lipid for use in a tumor treatment method. There is no written support whatsoever from the as-filed specification that applicant intends to claim polyamines and polyethyleninimes as a "cationic molecule", nor is there a sufficient disclosure from the as-filed specfication, either through illustrative examples or terminology, to teach those of ordinary skill how to make and

use the invention as broadly as it is claimed with respect to "cationic molecules" complexed with a CpG containing oligo as cancer treatment compositions. Given the fact the "cationic molecule" is generically claimed and is not limited in any way to any particularly named species, and given the fact that only cationic lipids are sufficiently disclosed in the specification, [the term "cationic molecules" can be reasonably construed as to embrace cationic molecules]

Applicant's reference to the prior art, which teaches the make and use of polyamines and polyethyleninimes as nucleic acid delivery vectors, is not the same as claiming a method of employing a "cationic molecule" in combination with a CpG motif containing oligo so as to effect a therapeutically anti-tumor effect.. The "large number of cationic molecules" that applicant refers to and that the specification incorporates by reference are drawn only to cationic lipids.

With respect to the breadth of "cationic lipid" as recited in claim 7 under the context of "eliminates the tumor", Applicant further asserts on page 6 bridging page 7 that numerous prior art teaches cationic lipids other than GL-76 can be used in combination with a nucleic to generate a therapeutic immune response in a tumor bearing mammal. However, the issue here is not that the examiner challenges a reasonable scope drawn to "a reduction of tumor burden" or "prolonged survival" wherein a cationic lipid complexed with a CpG motif containing nuclecic acid is employed in a tumor-bearing mammal. The Dow reference does not teach a cure of or elimination of an established tumor wherein a specifically named cationic lipid is employed, let alone a generic cationic lipid/DNA complex being employed as a master curing drug. Applicant's assertions together with the disclosures of the Dow references are not

sufficient to overcome the specific reasoning and doubts expressed in the art of record and as disclosed in details by the above stated rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

((e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

To the extent that the claimed invention embrace a method of generating a protective anti-tumor cell immune response in a mammal having a tumor, the method comprising the step of administering to a tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active nucleic acid sequence that does not encode for an expressible tumor-associated antigen, wherein said composition is administered in an amount effective to stimulate said protective anti-tumor cell immune response, thereby inhibiting the growth of the tumor,

The following rejections are applicable.

Claims 3-7, 9-16, 18, 20-22, and 24 are rejected under 35 USC 102(e) as being anticipated by Dow *et al* (US Pat No. 6,693,086).

Dow teaches essentially the claimed subject matter, namely a therapeutically anti-tumor composition comprising essentially a cationic lipid, and a CpG containing oligo or an isolated bacterially-derived nucleic acid vector without a gene insert, or a fragment thereof (see claim 1). Claim 4 of Dow recites that DOTAP, for example, is employed as a cationic lipid based carrier. As such, the oligo or nucleic acid vector does not encode for a tumor associated antigen. Column 15, par. 2 specifically recites that an elicited immune response is employed to treat a tumor, and column 16, last paragraph recites that the composition can be used to reduce the growth of a tumor. Column 17 bridging column 18 teaches that a CpG containing oligo or nucleic acid vector can be obtained from any source, including mammalian, bacterial, or viral sources. While Dow teaches that a DNA coding for a tumor associated antigen can be included, such is not necessary, since either a non-coding DNA or a cytokine coding DNA can be used to elicit an anti-tumor response.

For example, column 13 states:

> Therapeutic compositions useful in the method of the present invention include compositions containing nucleic acids having any nucleic acid sequence, including coding (i.e. encoding at least a portion of a protein or peptide) and/or non-coding (i.e., not encoding any portion of a protein or peptide) sequences, and including DNA and/or RNA. In the above-described embodiment of the present invention, since expression of a protein encoded by the nucleic acid molecule is not required for elicitation of a systemic, non-antigen-specific immune response, the molecule is not necessarily operatively linked to a

transcription control sequence. It is to be noted, however, that further advantages can be obtained (i.e., antigen-specific and enhanced immunity) by including in the composition a nucleic acid sequence (DNA or RNA), which encodes an immunogen and/or a cytokine.

Column 15 discloses that the claimed composition can be administered intraperitoneally into the liver or spleen and at other sites in the body intended for an elicitation of an immune response, second full par. Further, column 36 discloses that primary hepatic cancer and lung tumor can be treated therapeutically, and that the claimed composition can be administered into the lung or liver containing the tumor.

Absent evidence to the contrary, the method of Dow has all of the properties cited in the claims.

Claims 3-7, 9-16, 18, 20-22, and 24 are rejected under 35 USC 103 as being unpatentable over Krieg *et al.* (US Pat No. 6,207,646), Krieg (US Pat No. 6,218,371), or Krieg (US 6,429,199), each of which taken with Marshall (WO 98/02191) or Erabacher

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response against a tumor antigen present in a tumor bearing mammal when used in combination with a nucleic acid polymer including those non-expressible DNA containing CpG motifs nucleic acids, which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (The '646 patent, column 12, lines 25-34; the '371 patent, column 23 bridging column 24, column 24 second full par; the '199 patent, column 14 bridging column 15) can be employed in combination with a CpG motif containing non-expressible plasmid-derived (bacterial derived plasmid) nucleic acid

polymer as immunostimulatory nucleic acid complex (the ' 646 patent, column 12, lines 12-24, lines 49-50; the '371 patent, column 22, lines 15-17, lines 43-67, column 24, second full par., column 30, lines 15-18; the '199 patent, column 14, lines 48-53, column 22, lines 14-18); when employed for induction of an immune response to a target cancer antigen (the '646 patent, column 6, lines 55-56, column 10, lines 16-23 ; the '371 patent, column 7; the '199 patent, column 10, lines 27-31). The 646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64). Intravenous administration of the CpG containing nucleic acid polymer complexed with a deliver carrier such as a cationic lipid is also disclosed (the '646 patent, column 34, line 53; the '371 patent, column 31, last paragraph; the '199 patent, column 25, lines 36-38.

More specifically,

In the '199, column 4 states:

In one aspect the invention is a method for activating a dendritic cell. The method includes the steps of contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated CpG dinucleotide wherein the nucleic acid is from about 8–80 bases in length in an amount effective to activate a dendritic cell. In one embodiment the dendritic cell is an isolated dendritic cell.

The isolated nucleic acid is one which contains at least one unmethylated CpG dinucleotide and which is from about 8–80 bases in length. In one embodiment the unmethylated CpG dinucleotide has a formula:

$$5'N_1X_1CGX_2N_2 3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1 is adenine, guanine, or thymine; X_2 is cytosine, adenine, or thymine; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In another embodiment the unmethylated CpG dinucleotide has a formula:

$$5'N_1X_1X_2CGX_3X_4N3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1X_2 is selected from the group consisting of TpT, CpT, TpC, and ApT; X_3X_4 is selected from the group consisting of GpT,GpA, ApA and ApT; N is any nucleotide and N_1+N_2 is from about 0 25 nucleotides. In a preferred embodiment N_1 and N_2 of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In an illustrative embodiment the isolated nucleic acid is selected from the group consisting of SEQ ID NOS. 20, 24, and 38 46. In another embodiment the isolated nucleic acid is SEQ ID NO.: 84 or 85.

In yet another embodiment the nucleotide of the isolated nucleic acid has a phosphate backbone modification, such as, for example, a phosphorothioate or phosphorodithioate modification. In one embodiment the phosphate backbone modification occurs at the 5' end of the nucleic acid. Preferably the phosphate backbone modification occurs at the first two internucleotide linkages of the 5' end of the nucleic acid. According to another embodiment the phosphate backbone modification occurs at the 3' end of the nucleic acid. Preferably, the phosphate backbone modification occurs at the last five internucleotide linkages of the 3' end of the nucleic acid.

column 5 also states:

The isolated nucleic acid is one which contains at least one unmethylated CpG dinucleotide and which is from about 8 80 bases in length. In one embodiment the unmethylated CpG dinucleotide has a formula:

5'N,X,CGX,N,3'

wherein at least one nucleotide separates consecutive CpGs; X_1 is adenine, guanine, or thymine; X_2 is cytosine, adenine, or thymine; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In another embodiment the unmethylated CpG dinucleotide has a formula:

5'$NX_1X_2CGX_3X_4N$3'

wherein at least one nucleotide separates consecutive CpGs; X_1X_2 is selected from the group consisting of TpT, CpT, TpC, and ApT; X_3X_4 is selected from the group consisting of GpT,GpA, ApA and ApT; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In a preferred embodiment N_1 and N_2 of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In an illustrative embodiment the isolated nucleic acid is selected from the group consisting of SEQ ID Nos. 20, 24 and 38–46. In another embodiment the isolated nucleic acid is SEQ ID NO.: 84 or 85.

column 10 states:

activator.

The dendritic cells may also be contacted with CpG using in vivo methods. In order to accomplish this, CpG is administered directly to a subject in need of immunotherapy. The CpG may be administered in combination with an antigen or may be administered alone. In some embodiments, it is preferred that the CpG be administered in the local region of the tumor.

column 23:

In addition, an immunostimulatory oligonucleotide can be administered prior to, along with or after administration of a chemotherapy or immunotherapy to increase the responsiveness of the malignant cells to subsequent chemotherapy or immunotherapy or to speed the recovery of the bone marrow through induction of restorative cytokines such as GM-CSF. CpG nucleic acids also increase natural killer cell lytic activity and antibody dependent cellular cytotoxicity (ADCC). Induction of NK activity and ADCC may likewise be beneficial in cancer immunotherapy, alone or in conjunction with other treatments.

column 22 states:

For administration in vivo, nucleic acids may be associated with a molecule that results in higher affinity binding to target cell (e.g. dendritic cell) surfaces and/or increased cellular uptake by target cells to form a "nucleic acid delivery complex." Nucleic acids can be ionically, or covalently associated with appropriate molecules using techniques which are well known in the art. A variety of coupling or crosslinking agents can be used, for example protein A, carbodiimide, and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP). Nucleic acids can alternatively be encapsulated in liposomes or virosomes using well-known techniques.

Likewise, in the '371 patent,
Column 3 states:

The present invention relates to methods and products for inducing a synergistic immune response using a combination of a CpG oligonucleotide and a cytokine. In one aspect the invention is a method for stimulating an immune response in a subject. The method includes the steps of administering to a subject exposed to an antigen an effective amount for inducing a synergistic antigen specific immune response of an immunopotentiating cytokine and an immunostimulatory CpG oligonucleotide having a sequence including at least the following formula:

$$5' X_1CGX_2 3'$$

wherein the oligonucleotide includes at least 8 nucleotides wherein C and G are unmethylated and wherein X_1 and X_2 are nucleotides.

The cytokine may, for instance be GM-CSF, IL-3, IL-5, IL-12, or interferon-γ. The immunopotentiating cytokine may also be an antigen-cytokine fusion protein. In a preferred embodiment the antigen-cytokine fusion protein is an antigen-GM-CSF fusion protein.

column 6 states:

vivo and ex vivo. A synergistic increase in survival rate was even observed in animals having an established tumor. The method is performed by administering to the subject who has been exposed to an antigen an effective amount for inducing a synergistic antigen specific immune response of an immunopotentiating cytokine and an immunostimulatory CpG oligonucleotide.

The finding is based on the discovery that when an immunostimulatory CpG oligonucleotide is administered to a subject in combination with an immunopotentiating cytokine the resultant immune response is synergistic. Both CpG oligonucleotides and immunopotentiating cytokines have the ability to produce immune responses on their own when administered to a subject. When the combination of the two is administered together, however, the quantity and type of immune response shifts. For instance, when the CpG oligonucleotide and immunopotentiating cytokine are administered in conjunction with an antigen using repeat immunizations, as shown in FIG. 3, a synergistic induction in antigen specific IgG is observed. Additionally, when CpG and GM-CSF are administered together an antibody response develops that includes both IgG2a (indicative of a Th1 immune response) and IgG1 (indicative of a Th2 immune response) whereas when GM-CSF is administered alone IgG2a antibodies are undetectable or low depending on the strain of the animal.

Amazingly, the combination of a CpG oligonucleotide and immunopotentiating cytokine has a dramatic effect on the survival rate of animals injected with a tumor, even when administered several days after tumor inoculation. The finding was remarkable because it demonstrated that the combination of drugs was able to eliminate an established tumor. Typical prior art immunization strategies generally are performed prior to inoculation to prevent the establishment of a tumor. When mice were injected with a tumor and not provided with any subsequent tumor therapy the survival rate was 0%. Mice treated with CpG oligonucleotide alone or GM-CSF and antigen had survival rates of 0 and 30% respectively. The combination of CpG oligonucleotide and GM-CSF produced a dramatic survival rate of 70%. This finding has serious implications for the treatment of established tumors as well as for the prevention of tumor development.

The invention in one aspect is a method for stimulating an immune response in a subject. The method is performed by administering to the subject who has been exposed to an antigen an effective amount for inducing a synergistic antigen specific immune response of an immunopotentiating cytokine and an immunostimulatory CpG oligonucleotide.

column 8 states:

In the method of the invention, CpG oligonucleotide are used with an immunopotentiating cytokine. "Immunopotentiating cytokines" are those molecules and compounds which stimulate the humoral and/or cellular immune response. The term "cytokine" is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. Examples of cytokines include, but are not limited to IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, granulocyte-macrophage colony stimulating factor (G-MCSF), granulocyte colony stimulating factor (GCSF), interferon-γ (γ-INF), tumor necrosis factor (TNF), TGF-β, FLT-3 ligand, and CD40 ligand.

column 30 states:

In the method of the invention, CpG oligonucleotide are used with an immunopotentiating cytokine. "Immunopotentiating cytokines" are those molecules and compounds which stimulate the humoral and/or cellular immune response. The term "cytokine" is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. Examples of cytokines include, but are not limited to IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, granulocyte-macrophage colony stimulating factor (G-MCSF), granulocyte colony stimulating factor (GCSF), interferon-γ (γ-INF), tumor necrosis factor (TNF), TGF-β, FLT-3 ligand, and CD40 ligand.

Thus, the Krieg patents all teach that CpG containing oligo do not necessarily code any protein or antigen, and can be administered alone and can be administered in a delivery complex such as in liposome or cationic lipid based liposomes.

While the Krieg references do not teach explicitly protocols for the making and use cationic liposomes for use as a carrier to deliver a CpG containing oligo to a tumor bearing mammal as an anti-tumor composition, the Krieg references do teach CpG containing oligos when having a modified backbone would elicit an anti-tumor response, and that a liposome or cationic lipids can be incorporated for the delivery of the oligos. Further, the concept of employing a cationic lipid or liposome as a nucleic acid carrier and protocols for making lipid/nucleic acid complexes for use in therapeutic applications, are well established in the prior art at the time the invention was made. Indeed, the Marshall and Erabacher references is some of many exemplified references that teach such protocols are routinely employed in the prior art. More specifically, Marshall (entire disclosure) teaches that cationic lipids are effective carriers of nucleic acid molecules for use in an *in vivo* nucleic acid delivery or transfer to target cells. Detailed teachings with respect to the how to make and use of cationic lipid/DNA complexes as therapeutic compositons are disclosed in Marshall. Erabacher teaches a method of employing a cationic lipid complex composed mainly of a cytofectin-based cationic lipid/CpG containing plasmid fragments for use in therapeutic vaccine (entire disclosure, particularly, page 4, par. 0090 and 0091. Intravenous administration of the complex is disclosed on page 0102.

Thus, it would have been obvious for one of ordinary skill in the art, with a relatively high skill level, to employ a cationic lipid as an effective carrier to deliver the CpG containing plasmid of Krieg

to a tumor bearing mammal for the purpose of therapeutically inhibiting the growth of the tumor as the result of an elicitation of the immune response by the CpG containing oligo. One would have expected that by employing a cationic lipid to enhance the delivery of a nucleic acid to a tumor target site, as taught by Marshall and Erabacher, the CpG containing DNA are expected to exert its intended biological activity such as an elicitation of an immune response at the tumor target site.

Thus, the claimed invention was *prima facie* obvious.

Applicant's response (pages 7-9) has been considered by the examiner but is not found persuasive because of the new grounds of rejection. To the extent that the assertions are relevant to the above grounds of rejection, such are also not found persuasive. More specifically, applicant asserts that the Krieg patents are not enabling for the make and use of the claimed invention as claimed. However, such is an expressed opinion without any evidential support, and thus, is not found persuasive so as to overcome the grounds of rejection. Furthermore, the totality of the prior art of record as a whole does teach, provide and suggest a motivation to employ a cationic lipid as an effective carrier for a DNA for use as a tumor treatment composition. Applicant further argues that because of example 5, and Figure 5 of the '371 patent, which teaches a naked administration of exemplified CpG containing oligos to mice does not exert any anti-tumor treatment effect, the '371 patent does not teach disclose a method to treat a tumor bearing mammal. Applicant's analysis of Example 5 is not accurate because Krieg(s) all teach that a cationic lipid/CpG containing oligo rather than a naked CpG containing oligo is employed in a cancer treatment effect as taught in the '371 patent. In other words, the examiner does not rely upon example 5 or Figure 5 for the anticipation. Such is not sufficient to address all of the limitations as recited in the currently amended claims. In fact, the combined teachings provided by any of Krieg(s), and not just Krieg in

'371 patent, and Erabacher would provide a sufficient teaching to make and use the claimed invention with a reasonable expectation of success. Note also that the claims do not exclude *per se* the use of a recombinant antigen or cytokine in the claimed compositions. In fact, the '371 patent teaches by employing a cytokine together with a CpG containing oligo, a synergistic cancer treatment effect is generated.

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731.**

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER